The safety and efficacy of radium-223 dichloride for the treatment of advanced prostate cancer

James M. Wilson & Christopher Parker

Department of Radiotherapy and Urology, The Royal Marsden Hospital, Sutton UK

Correspondence to chris.parker@icr.ac.uk

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Abstract

Introduction: A number of drugs have been shown to extend life expectancy in castration-resistant prostate cancer (CRPC). Skeletal related events (SREs) secondary to bone metastases cause significant morbidity for men with CRPC. The α-emitting radiopharmaceutical radium-223 dichloride has been shown to improve overall survival, time to symptomatic skeletal events (SSEs) and quality of life in CRPC.

Areas covered: The development of radium-223 from pre-clinical studies to the evidence of efficacy and safety from a phase 3 trial is discussed as well as its pharmacokinetics and metabolism. The integration of radium-223 into routine care for patients with advanced prostate cancer is included including a comparison with other agents in this setting.

Expert commentary: The risk/benefit ratio for radium-223 is very similar to that of other agents used in the CRPC setting and is a treatment option for men unsuitable for cytotoxic chemotherapy because of comorbidities. The ALSYMPCA trial demonstrated an improvement in SSEs with radium-223. This is a clinically relevant end-point as not all radiologically-detected SREs are apparent to patients. The correct sequencing of the life-prolonging treatments available to men with CRPC is subject to debate. Radium-223 therapy should be considered before the development of visceral metastases. Drug-combination studies are underway.

Introduction

Worldwide, over 1.1 million men are diagnosed with prostate cancer each year and it is the most frequently diagnosed cancer in men in the developed world [1]. When prostate cancer metastasizes, it preferentially spreads to bone. The mainstay of treatment for metastatic prostate cancer is androgen deprivation. When the disease progresses despite maximum androgen blockade, the patient is said to have castration-resistant prostate cancer (CRPC). Bone metastases occur in more than 90% of patients with CRPC [2]. Median overall survival (OS) for men with bony metastatic CRPC treated with modern therapies is approaching 3 years [3,4]. Furthermore, bone metastases can lead to pathological fractures, spinal cord compression [SCC], the need for surgical intervention, or radiotherapy. These are often referred to as skeletal-related events (SREs). SREs reduce quality of life and OS and increase treatment costs [5–7]. While bone-targeting therapies such as bisphosphonates and denosumab have been shown to delay the time to an SRE, an improvement in OS or quality of life with these agents has not been demonstrated [8–10].

The therapeutic application of radiopharmaceuticals that can be incorporated into hydroxyapatite, a bone's inorganic matrix, and therefore deliver a radiation dose to bone metastases, has been explored extensively. The first bone-targeting radiopharmaceuticals to be licensed for clinical use were the β-emitters ^{89}Sr (Metastron®, GE Healthcare) and ^{153}Sm-etyhylene diamine *N*,*N*-tetramethylene phosphonic acid (Quadramet®, EUSA Pharma). As β-emitters have a track length in the order of millimeters, their use for the palliation of bone pain from metastases has been limited by bone marrow toxicity. For example, in a trial comparing ^{89}Sr with placebo, grade 2+ thrombocytopenia was seen in 61% compared to only 10% of patients receiving placebo [11]. Their use was therefore limited to the palliation of bone pain in selected patients.

The use of α-emitters was therefore explored as they deliver high-linear energy transfer radiation over a track length of less than 100 μm. This might allow lethal double-strand DNA breaks in cancer cells while limiting the radiation delivered to normal tissues, including the bone marrow. This hypothesis was confirmed in preclinical experiments that demonstrated an increase in the estimated absorbed dose at the bone surface compared to the bone marrow with ^{223}Ra and ^{211}At (α-emitters) compared to ^{89}Sr or ^{131}I (β-emitters) [12,13].

Radium, like calcium, is an alkaline earth element that is absorbed into bone matrix at sites of active mineralization [14]. Radium compounds have been used as bone-seeking radiopharmaceuticals for some time, with considerable experience in the use of ^{224}Ra in the treatment of ankylosing spondylitis [15,16]. Because of the short half-life of ^{224}Ra and concerns about how it decays, including via its gaseous daughter radionuclide ^{220}Ra, which rapidly dissociates from bone, ^{224}Ra has not been developed further for clinical use. The half-life of ^{223}Ra is approximately three times that of ^{224}Ra ($t_{1/2}$ = 11.4 days), leading to interest in its use in cancer treatment as the drug can be delivered to the site of bone disease and continue to deliver dose. Radium-223 dichloride ($^{223}RaCl_2$, radium-223) was developed by Algeta ASA (Norway) and Bayer (Germany) under the trade names Alpharadin® and subsequently Xofigo®. Radium-223 decays to the stable isotope of lead, ^{207}Pb, in six steps. Of the energy emitted in

this process, 95.3% comes from alpha radiation with 3.6% and 1.1% coming from beta and gamma radiations, respectively [17]. It is possible to detect photon emissions from the decay of radium-223 using standard techniques. The incorporation of radium-223 into bone and its potential use in targeting bone metastases while sparing bone marrow because of the favorable path length of the emitted radiation is illustrated in Figure 1. Preclinical data was obtained to support the development of radium-223 for clinical use in a rat metastatic breast cancer model. In this experiment, a significant improvement in symptom-free survival was observed with treatment with ≥10 kBq/kg of radium-223. No weight loss or bone marrow toxicity was seen in the treated rats or in mice treated with 1 MBq/ml in a parallel experiment [18].

Radium-223: pharmacokinetics, pharmacodynamics, and metabolism

Following intravenous injection, radium-223 is cleared rapidly from the blood, with only 6% of initial activity seen in the blood by 1-hour post injection, falling to less than 1% of the injected activity at 24 hours [19]. Excretion is predominantly via the gastrointestinal tract via the small bowel with little (approximately 5%) early urinary excretion [20]. This observation led the authors to speculate that any treatment-associated diarrhea may be the result of small bowel radiation dose during excretion.

Further confidence in the clinical use of radium-223 was added by the observation that there was little redistribution of daughter nuclides from bone after uptake [13]. Bone uptake increases with time up to 24 hours, and then there is almost no redistribution of the daughter nuclides. This longer half-life makes it more likely that the radium isotope will be incorporated into bone before decay, reducing the dose of radiation delivered to normal tissues while the isotope is distributed, taken up, and eliminated. Evidence that radium-223 accumulates in the bones has been demonstrated by scintigraphy in six patients. Accumulation of radium-223 was observed in the skeleton, particularly in areas of osteoblastic metastases in a similar pattern to that observed on ^{99m}Tc-methylene diphosphonate bone scans [19]. Uptake in bone has been demonstrated as early as 10 minutes following injection. Once radium-223 leaves the circulation, its daughter nuclides are only ever noted in the bone and gastrointestinal tract [20] – unlike the decay products of ^{224}Ra and ^{225}Ra, which have been shown to redistribute into the kidneys [21,22].

Dauer *et al*. demonstrated low external dose rates from patients treated with radium-223, allowing for patient release from radiation control measures immediately following administration when doses of up to 100 kBq/kg were used [23]. Surface doses from vials and syringes containing radium-223 are lower than other radiopharmaceuticals and can therefore be delivered using standard nuclear medicine equipment. After injection, the mean measured normalized dose rate per injected activity at 1 m from the patient was 0.02 μSv h^{-1} injected MBq^{-1}. No restrictions on family contact therefore have to be made after treatment with radium-223. The vast majority of radium-223 was excreted via the gastrointestinal tract into the feces. As there is also some blood and urine activity, the authors recommend caution with body fluids and stool for 1 week after drug injection. The low range of alpha radiation and the observation that by 1 week post injection most of the remaining activity is bound to bone means that no extra precautions are required for burials within 2 months of drug delivery and that

local rules for surgical and postmortem intervention should be followed, with biological waste being disposed of appropriately.

Studies of the efficacy and safety of radium-223 in CRPC

Phase 1 studies

The first Phase 1 experience with radium-223 was in a cohort of 25 patients with bone metastases (15 prostate cancer, 10 breast cancer) who entered into a dose-escalation study. Five dose levels ranging from 46 to 250 kBq/kg were tested, with five patients in each cohort [19]. While no dose-response relationship was seen, a reduction in pain scores was observed in 52%, 60%, and 56% at 1, 4, and 8 weeks post injection, respectively. A transient worsening of pain in the first week of treatment was noted in seven of the patients. A greater reduction in alkaline phosphatase (ALP) was seen in patients with prostate cancer compared to those with breast cancer (a mean decrease of 52.1% vs. 29.5%, $p = 0.0028$), with the greatest reduction in patients with an elevated ALP prior to treatment. These promising results led to the recommendation that a placebo-controlled Phase II study of radium-223 should be initiated. As the reduction in ALP was similar across all of the dose levels, 50 kBq/kg (the lowest tested dose) was recommended for use in future studies, despite no dose-limiting toxicity being observed at higher doses.

A tendency to myelosuppression was noted as the treatment dose increased. Grade 1 thrombocytopenia was seen in three patients, with no toxicity greater than grade 1. This is in contrast to the clinically significant thrombocytopenia observed in treatment with β-emitters. Two patients experienced grade 3 neutropenia and three patients had grade 3 leucopenia. All observed adverse events (AEs) were graded as mild to moderate. Ten of the 25 patients had diarrhea and nine experienced bone pain including bone ‘flare’. Fatigue, nausea, and vomiting were seen in five patients each – with four of five patients in the highest dose group experiencing nausea.

In another Phase I study of 11 patients treated with 50–100 kBq/kg of radium-223, six of whom received a second treatment of 50 kBq/kg 6 weeks later, no dose-limiting toxicity occurred [20]. While a trend toward myelosuppression at higher doses was seen, there was no grade 3+ thrombocytopenia and only one incidence of grade 3 neutropenia. Some promising pharmacodynamic effects were noted, including a reduction in serum PSA in 5 out of 10 patients. Eight patients had a >30% decline in bone-specific ALP (b-ALP) and one had a >50% decline. Seven of 10 patients also demonstrated a reduction in N-telopeptides, a marker of bone turnover.

Phase II studies

A Phase II study in men with metastatic CRPC tested the activity of radium-223 in terms of reduction in b-ALP concentration and time to occurrence of SREs [24]. A randomized, placebo-controlled trial design was chosen. Treatment was started at, or within 7 days of, the start of external-beam radiotherapy (EBRT) to the most painful

site of bone disease. Participants received monthly injections for 4 months with radium-223 or placebo. Sixty-four patients were recruited, with safety data available for all patients. There were fewer serious AEs (SAEs) in patients receiving radium-223 than placebo and no patients discontinued radium-223 because of treatment-related toxicity. However, perhaps surprisingly given the route of elimination of radium-223, constipation was noted in 12 of the 33 patients (mild to moderate in 11 patients) treated with radium-223 and only in two patients receiving placebo. This was the only AE that was statistically different between the two groups and did not appear to be temporally related to treatment. One patient treated with radium-223 was admitted to hospital because of vomiting after the first injection, but this did not recur with subsequent treatment. No cumulative hematological toxicity was noted and grade 2+ neutropenia was noted in only three patients given radium-223.

Radium-223 was shown to have a favorable effect on the biochemical end points of this study, but changes in the time to an SRE did not reach statistical significance. The median change in b-ALP seen 4 weeks after completing treatment was −65.9% (95% confidence interval [CI] −69.5 to −57.7) in the radium-223 group compared to 9.3% (3.8 to 60.9) in those receiving placebo ($p < 0.0001$). A greater relative reduction in the serum prostate-specific antigen (PSA) was noted in the radium-223 group (−23.8%, range −98.6 to 545.6) than the placebo group (44.9%, range −91.3 to 563.5) ($p = 0.003$). The median time to PSA progression was also prolonged in the radium-223 group (26 compared to 8 weeks, $p = 0.048$). The difference in time to SRE in the radium-223 and placebo groups (14 vs. 11 weeks) was not statistically significant. Interestingly, an improvement in OS was observed with radium-223 therapy compared to placebo. Median OS was 65.3 weeks compared to 46.4 weeks. The hazard ratio (HR) for survival was 2.12 (95% CI 1.13–3.98, $p = 0.020$), favoring treatment with radium-223 and supporting its ongoing use in clinical studies.

Another Phase 2 study demonstrated a dose-dependent effect of radium-223 on serum PSA and ALP [25]. A total of 122 patients were randomized to 25, 50, and 80 kBq/kg of radium-223 given every 6 weeks for three injections. A ≥50% reduction in PSA was noted in no patients (0%), two patients (6%), and five patients (13%) receiving 25, 50, and 80 kBq/kg of radium-223, respectively. A statistically significant difference in ALP response was noted between the 25 and 50 kBq/kg groups and the 25 and 80 kBq/kg groups, but not the 50 and 80 kBq/kg treatment groups. There was no statistically significant difference in the incidence of symptomatic SREs or changes in pain score between the three groups. There was no apparent dose-response effect with respect to AEs, except for a trend to an increase in gastrointestinal AEs. Diarrhea and nausea occurred in 21% and 16% of patients, respectively. SAEs were rare with bone pain in one patient in the 50 kBq/kg group and bone pain, muscle weakness, and constipation in one patient each in the 80 kBq/kg group. There was no difference in hematological parameters between the dose levels, but hemoglobin was shown to decrease from baseline to month 24. No difference in the proportion of patients who died or the time to death was demonstrated between dose groups. Based in part on these data, 50 kBq/kg was chosen as the dose for further clinical evaluation.

Phase III studies

The Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) study was a phase 3, randomized, double-blind study comparing the efficacy and safety of radium-223 with placebo in men with CRPC and bone metastases [26]. Patients with progressive CRPC, two or more bone metastases in the absence of visceral disease or malignant lymphadenopathy >3 cm in the short axis, and an Eastern Cooperative Oncology Group (ECOG) performance status 0–2 were eligible for study entry. Patients were required to have symptomatic disease, use analgesia regularly or to have received EBRT for bone pain within 12 weeks of study entry. Only patients who had received docetaxel or were not healthy enough or had declined docetaxel were eligible to participate in the ALSYMPCA study. Patients were randomized 2:1 to receive 50 kBq/kg of radium-223 and best supportive care (BSC) or placebo and BSC every 4 weeks to a total of six injections. Patients were stratified according to: previous docetaxel treatment or not, baseline ALP <220 U/L or >220 U/L, and current bisphosphonate use or not. OS was the primary end point. Secondary end points were time to a ≥25% increase in ALP, total ALP response (≥30% from baseline), normalization of ALP, time to the first symptomatic skeletal event (SSE), and time to PSA progression. Safety and quality of life (Functional Assessment of Cancer Therapy – Prostate; FACT-P) end points were also included. The ALSYMPCA trial was different from other trials of bone-targeting agents in that it was concerned only with symptomatic SREs and not asymptomatic bone fractures that are detected on follow-up imaging. It also allowed patients in both groups to receive best standard of care at the discretion of the treating physician, which makes the study findings easier to generalize to clinical practice. On the recommendation of an independent data and safety monitoring committee, the ALSYMPCA study was stopped at a planned interim analysis after 528 deaths because of a demonstrable survival advantage with radium-223 and an acceptable safety profile. The final report of the trial therefore provides a descriptive analysis of efficacy and safety of radium-223 before crossover of treatment.

At the interim analysis that led to the early closure of the trial, median OS was 14.0 months in the radium-223 group compared to 11.2 months in the placebo group. This is a 30% reduction in the risk of death (HR 0.70; 95% confidence interval 0.55–0.88; $P = 0.002$). This was altered to 14.9 and 11.3 months in the radium-223 and placebo groups, respectively, when the analysis was updated, with extended follow-up confirming the 30% reduction in the risk of death with radium-223 therapy (HR 0.7.; 95% CI 0.58–0.83; $P < 0.001$).

More patients in the radium-223 group demonstrated a ≥30% reduction in the total ALP and PSA than in the placebo group. A significant prolongation in the time to an increase in ALP was seen with radium-223 compared to placebo (7.4 vs. 3.8 months, respectively; HR 0.17; 95% CI 0.13–0.22; $P < 0.001$). There was not a significant difference in the time to PSA progression in the two groups.

Radium-223 appears to be well tolerated by patients, with 63% receiving all six injections compared to only 47% in the placebo group. Additionally, the percentage of patients' AEs was consistently lower in the radium-223 group versus the placebo group. Grade 3 or 4 AEs were also lower in the radium-223 group (56% of patients) than the placebo group (62%) A low incidence of myelosuppression was observed

(Grade 3/4 neutropenia in 1.8% and 0.8%, anemia in 10.4% and 15.0%, and thrombocytopenia in 4.1% and 1.6% of the radium-223 and placebo groups, respectively). One patient in each group experienced febrile neutropenia (<1%).

More patients had a meaningful improvement in quality of life as defined by an increase of ≥10 points on a scale of 0–156 on the FACT-P questionnaire (25% vs. 16% for radium-223 and placebo respectively; *P* = 0.02).

In Phase III trials in patients with CRPC, ALSYMPCA was unique in so far as it allowed both patients who had received docetaxel to be recruited as well as those who had not (although the expectation was that the patients would not go on to receive docetaxel). A subsequent, preplanned subgroup analysis of the ALSYMPCA trial assessed the impact of previous docetaxel use on the efficacy and safety of radium-223 [27]. Of the 921 patients recruited to ALYMPCA, 526 (57%) had received docetaxel and 395 (43%) had not. Patients who had already received docetaxel had a median age of 69 years compared to 74 years in the no previous docetaxel group. Of the 599 patients treated with radium-223, 347 (58%) had previously received docetaxel while 253 (42%) had not. 17.1% of patients with previous docetaxel use were older than 75, compared to 43.3% of the no previous docetaxel group. Radium-223 use was shown to prolong OS compared to placebo irrespective of previous docetaxel use (HR 0.70; 95% CI 0.56–0.88 for patients who had previously received docetaxel and a HR 0.69; 95% CI 0.52–0.92 in the no previous docetaxel subgroup).

Data on the number of cycles of docetaxel the patients recruited to ALSYMPCA had received is lacking. This information may have added a more detailed interpretation of the small, but a statistically significant increase in hematological toxicity observed in patients pretreated with docetaxel. Patients who had not received docetaxel either declined this treatment or were deemed unsuitable for docetaxel. The reasons for patients not receiving docetaxel may also contribute to toxicity with radium-223, so the results of this subgroup analysis should be interpreted with caution. The patients previously treated with docetaxel had a higher incidence of AEs in both the placebo and radium-223 arms compared to those who had not received docetaxel. Of note, grade 3–4 thrombocytopenia was higher in the previous docetaxel group than the no prior docetaxel groups (9% vs. 3%). Of the patients who received radium-223, more blood transfusions were seen in the previous docetaxel group compared to the no docetaxel group (26% vs. 18% between randomization and the end of treatment, 30% vs. 15% in the first 13 weeks following treatment, and 19% vs. 10% from the 13 weeks following treatment to the end of the study). This may represent an effect of docetaxel on the bone marrow or patient-specific factors such as more advanced disease in patients already treated with docetaxel.

A detailed analysis of the secondary end point data regarding the effect of radium-223 on SSEs was presented separately from the survival data [28]. The use of SSEs rather than SREs as an end point in the ALSYMPCA trial is an important distinction. SREs are historically used in clinical trials and are detected on periodic radiological review. Using SSEs, describing patients' symptoms, is a more clinically relevant end point. The time to first SSE was longer with radium-223 than with placebo (median time 15.6 vs. 9.8 months, HR 0.66; 95% CI 0.52–0.83; *p* = 0.0004). The number needed to treat with radium-223 to prevent one SSE was 7.6 (95% CI 4.9–16.4). In a *post hoc* analysis, the median SSE-free survival was significantly longer with radium-223 than

with placebo (9.0 vs. 6.4 months; $p < 0.0001$), as was the median time to a subsequent SSE (16.5 vs. 10.1 months; $p = 0.0004$). In a multivariate analysis of time to first SSE, radium-223 reduced the risk with a HR of 0.65 (95% CI 0.51–0.82; $p < 0.001$). The treatment effect of radium-223 was independent of other baseline variables, including the use of bisphosphonates at study entry. Other baseline factors that reduced the risk of an SSE were the current use of a bisphosphonate, extent of disease, and the WHO ladder for cancer pain score. Previous use of docetaxel increased the HR of SSE (1.39; 95% CI 1.08–1.80). Of note, radium-223 therapy reduced the incidence of SCC and the need for EBRT for bone pain. Four percent of patients in the radium-223 group and 7% of patients in the placebo group experienced SCC ($p = 0.03$; HR 0.52; 95% CI 0.29–0.93). Thirty percent of patients who received radium-223 required EBRT compared to 34% in the placebo arm ($p = 0.001$). The increased benefit of radium-223 on SSEs in patients receiving bisphosphates could be explained by an additive effect of the treatments, perhaps with bisphosphonates increasing radiation dose deposition by improving radium-223 uptake into the bone matrix [29,30].

It is important to note that with respect to symptoms, the inclusion criteria for the ALSYMPCA trial were broad, requiring the patients to have either regular analgesia or recent palliative radiotherapy. Thus, the trial included patients who were pain-free on simple analgesia or after recent radiotherapy. A subsequent subgroup analysis has shown that an OS survival benefit is seen in both patients requiring opioid analgesia prior to starting radium-223 therapy and those who do not require opioids (nonopioid subgroup: HR = 0.56, 95% CI: 0.39–0.82, $p = 0.002$; opioid subgroup: HR = 0.72, 95% CI: 0.53–0.98, $p = 0.038$) [31]. It could therefore be inferred that symptom severity is not an important consideration regarding the timing of radium-223.

Conclusion

Radium-223 represents an important advance in the treatment of CRPC. Radium-223 offers a substantial improvement in OS with a highly favorable safety profile. Radium-223 delays SSEs by a median of 6 months. For most patients, radium-223 has few or no side effects. For many patients, radium-223 dramatically improves pain control and improves quality of life. Unlike all other new drugs for CRPC, radium-223 has been shown to be both safe and effective in patients who are not suitable for chemotherapy.

Expert commentary

ALSYMPCA showed that radium-223 improves OS for men with CRPC by 30% (HR: 0.70 (95% CI: 0.55–0.88)). This is very similar to the magnitude of benefit from the other new drugs that have been approved for CRPC and which are now in routine clinical practice (docetaxel, sipuleucel-T, cabazitaxel, abiraterone, and enzalutamide; see Table 1).

We suspect that the ALSYMPCA results underestimate the true benefit of radium-223 on survival. Only around two-thirds of men in the trial completed all six cycles of radium-223. The trial was blinded so patients did not know whether they were getting

radium-223 or placebo. Furthermore, they did not know whether or not radium-223 was effective. A significant minority of patients may have stopped study drug because they were uncomfortable with their PSA rising and the possibility that they were receiving an inactive therapy. In routine clinical practice, compliance with radium-223 will be better, now that it is known to be safe and effective and with only a modest PSA response rate.

Risk/benefit ratio

In our opinion, the risk/benefit ratio for radium-223 is very similar to that of abiraterone and enzalutamide, and superior to that of docetaxel and cabazitaxel: The survival benefit associated with abiraterone, enzalutamide, and radium-223 is achieved with very little downside. Remarkably, in each of the pivotal phase III trials of these three agents, the experimental arm of the trial had fewer AEs and fewer SAEs than the control arm [3,4,32,33]. This is an extraordinary observation in clinical trials of new drugs, and indicates that abiraterone, enzalutamide, and radium-223 are not only effective but also very well tolerated. Not surprisingly, given their favorable toxicity profile, each of these three drugs has a proven benefit in quality of life as well as OS. By contrast, docetaxel and cabazitaxel have a less favorable toxicity profile, with an excess of AEs and SAEs, and in the case of cabazitaxel there is no data on quality of life [35]. Sipuleucel-T, while well tolerated, has no proven impact on quality of life.

Unmet needs

ALSYMPCA differed from the other pivotal phase III trials in CRPC in several ways. For example, the patient population included men who were chemotherapy-naïve but who were not expected to get chemotherapy. This group accounts for around 50% of all men with CRPC. Typically, these men are older (the average age of death from prostate cancer is 80 years), or have comorbidities that make them unfit for chemotherapy. They have not been included in other phase III trials, and represent an important area of unmet clinical need. They are unfit for treatment with docetaxel and cabazitaxel. Given their limited treatment options, radium-223 represents an important, clinically relevant advance for this group of patients.

Symptomatic skeletal events

One of the main secondary end points in the ALSYMPCA trial was time to first SSE. This end point should be contrasted with time to first SRE used in many other CRPC clinical trials. Both zoledronate and denosumab have been approved for use by virtue of their efficacy with respect to time to SRE. However, the use of SREs as an end point has been criticized because not all SREs are clinically important. In particular, fractures picked up on routine imaging are classed as SREs, but may not be apparent to the patient. In ALSYMPCA, there was no routine imaging, and fractures were only detected if symptomatic. Thus, an improvement in time to first SSE (as seen for

radium-223 in ALSYMPCA) is more clinically relevant than an improvement in time to first SRE (as seen with other bone targeting agents such as zoledronate and denosumab).

Other secondary efficacy end points

In ALSYMPCA, radium-223 was statistically superior to placebo with respect to all the secondary efficacy end points, including quality of life measured using FACT-P [36]. This benefit was seen with respect to almost all of the subscales of FACT-P, indicating a statistically significant benefit not just in terms of prostate cancer score, but also in terms of functional, emotional, and physical well-being. The most significant benefits were seen with regard to the four pain-related questions: Pain improved in patients treated with radium-223 and deteriorated in patients treated with placebo (mean change in pain from baseline, $p = 0.006$).

Other secondary efficacy end points

It is always difficult to compare quality of life results in one trial with those from a different trial. It is particularly difficult to compare the quality of life results from ALSYMPCA with those from other trials. For one thing, quality of life was measured relatively infrequently in ALSYMPCA. For another, radium-223 seldom leads to a PSA response. Many CRPC patients are acutely aware of their PSA level, and feel greatly encouraged (rightly or wrongly) when it falls. Thus, androgen receptor targeted drugs, which lead to profound PSA declines, may appear to have a relatively large impact on quality of life.

Safety

Radium-223 is extremely well tolerated. ALSYMPCA was a truly blinded trial because there was no immediately apparent difference in toxicity profile between radium and placebo. Typically, no concomitant medication is required to deal with side effects. Hematologic toxicity is rarely seen with radium-223 therapy. The hematologic safety profile is far more favorable than that of docetaxel or cabazitaxel (e.g. Grade 3+ neutropenia: 3% for radium-223 versus 82% for cabazitaxel).

Sequencing

The correct sequencing of the treatments available to men with advanced prostate cancer is subject to debate. It is important to ensure that patients access all available survival-prolonging treatments, including novel hormone therapy, radium-223, and taxane chemotherapy. It is not clear if all six cycles of radium-223 are required to confer a survival advantage, but this was the regimen tested in ASLYMPCA and so

should be regarded as the current standard. Care should be taken not to leave treatment with radium-223 too late in the patient pathway. Patients become ineligible for radium-223, but not chemotherapy, if they develop visceral metastases.

Five-year view

As the mechanism of action of radium-223 does not overlap with other treatments for CRPC (enzalutamide, abiraterone, docetaxel, and cabazitaxel), it is suitable for both sequencing and combination studies. This is an important next step in using radium-223 to improve outcomes for patients with CRPC.

While the use of radium-223 has been shown to be safe and effective irrespective of prior docetaxel use, the optimal sequencing of these treatments is not yet known. These data also need to be interpreted in the context of emerging evidence of benefit of docetaxel in the hormone-sensitive prostate cancer setting [37,38]. A potential clinical benefit of radium-223 in the hormone-naïve setting is yet to be investigated. Abiraterone and enzalutamide were not approved for use at the time the ALSYMPCA study was designed. However, given that radium-223 was used in ALSYMPCA in combination with the best available hormone therapy at the time, it seems very logical to use radium-223 in combination with abiraterone or enzalutamide. Phase 3 studies are already underway exploring the impact of combining radium-223 with abiraterone (ERA 223, NCT02043678) or enzalutamide (PEACE III, NCT02194842).

A Phase 1/2a study is investigating the safety and efficacy of combining radium-223 with docetaxel (NCT01106352). Overlapping toxicity, in terms of myelosuppression, makes this combination less attractive than with the hormonal agents. The integration of radium-223 with immunotherapies such as immune-checkpoint inhibitors and vaccines has also been suggested [34]. A Phase 2 study of Sipuleucel-T with or without radium-223 is currently open to recruitment (NCT02463799).

Although the standard radium-223 dose schedule of 50 kBq/kg every 4 weeks for six cycles has been shown to be effective and well tolerated, it is unlikely that this is the optimum dose schedule. A study exploring the benefit of re-treating with radium-223 in patients who have already received six cycles of treatment is underway (NCT01934790). Another randomized trial is comparing 50 versus 80 kBq/kg.

Given the mechanism of bone targeting of radium-223, it is likely that it will have activity against other cancers. There is some interest in extending the treatment indications for radium-223 with a Phase 1/2 study in patients with osteosarcoma (NCT01833520) and Phase 2 studies in bone-predominant metastatic breast cancer (NCT01070485) and metastatic radioiodine-refractory thyroid cancer (NCT02390934).

Key issues

- Radium-223 is an α-emitting radiopharmaceutical that can be incorporated into the bone's inorganic matrix at the site of active mineralisation.
- The short path-length of the emitted radiation causes lethal damage to cancer cells in bone metastases while sparing the bone marrow (see Figure 1).
- Radium-223 (50 kBq/kg q. 4 weeks for 6 cycles) and best supportive care improves overall survival compared to best supportive care alone (median OS 14.9 vs 11.3 months, HR 0.70; 95% CI 0.58 to 0.83; P < 0.001).
- Radium-223 is well-tolerated by patients. In the ALSYMPCA phase 3 trial, adverse events were more common in the placebo group than the patients receiving active treatment. Patients receiving radium-223 had an improvement in quality of life.
- An improvement in median OS is seen with radium-223 irrespective of previous docetaxel use.
- Treatment with radium-223 prolongs the time to a symptomatic skeletal event (median time 15.6 months vs 9.8 months, HR 0.66; 95% CI 0.52 to 0.83; p = 0.0004).
- Radium-223 reduces the risk of metastatic spinal cord compression.
- In the ALSYMPCA Phase III trial, radium-223 was used in combination with the best available hormone therapy. It would therefore seem logical to consider combination of radium-223 with abiraterone or enzalutamide. However, this has not formally been tested. Trials investigating the use of radium-223 in combination with new androgen receptor targeted agents are currently underway."

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Figure 1. Radium-223 is an alpha-pharmaceutical that targets bone metastases.

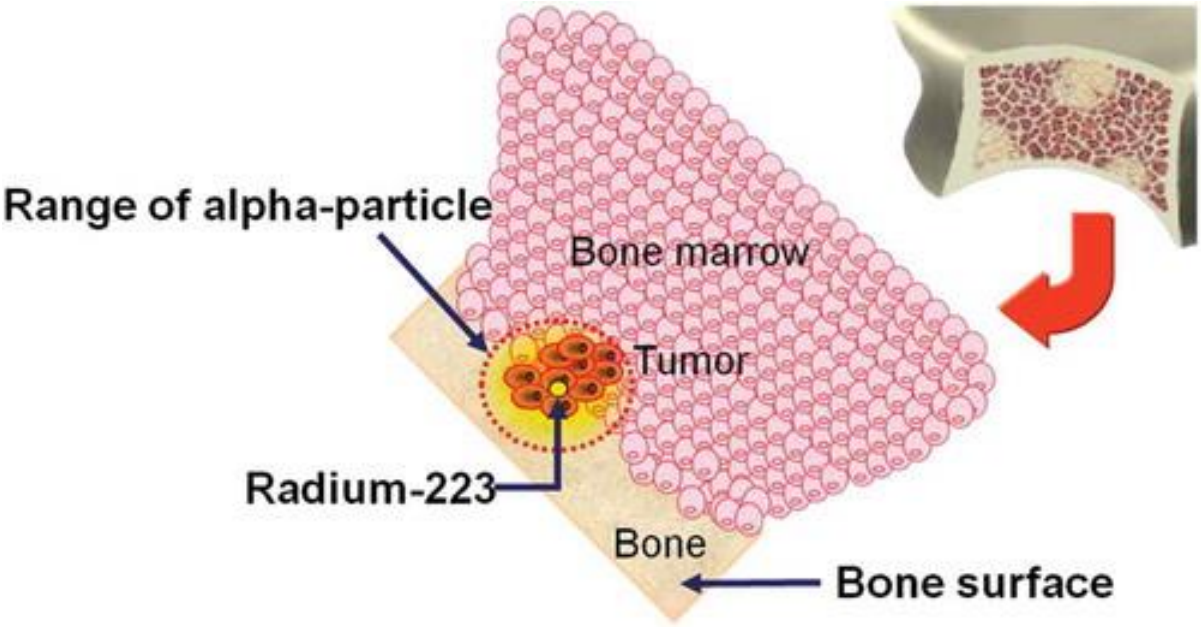

Table 1. A summary of recent Phase 3 trials in CRPC.

	Study name	Treatment	Control	Median OS (months; treatment vs. control)	Hazard ratio	95% confidence interval	*P*-value	Grade 3+ toxicities increased compared to control (>5%)
Pre- and post-docetaxel	ALSYMPCA [24]	Radium-223 and BSC	BSC	14.0 vs. 11.2	0.70	0.55–0.88	0.002	
Previous docetaxel	TROPIC [32]	Cabazitaxel and prednisolone	Mitoxantrone/prednisolone	15.1 vs. 12.7	0.70	0.59–0.83	<0.0001)	Neutropenia, febrile neutropenia, leukopenia, anemia, diarrhea, fatigue, asthenia
	AFFIRM [31]	Enzalutamide	Placebo	18.4 vs. 13.6	0.63	0.53–0.75	<0.001	
	COU-AA-301 [33,34]	Abiraterone and prednisolone	Prednisolone	15.8 vs. 11.2	0.74	0.64–0.86	<0.0001	
	ALSYMPCA [25]	Radium-223 and BSC	BSC	14.4 vs. 11.3	0.70	0.56–0.88	0.002	
No previous docetaxel	PREVAIL [30]	Enzalutamide	Placebo	32.4 vs. 30.2	0.71	0.60–0.84	<0.001	
	COU-AA-302 [29,39]	Abiraterone and prednisolone	Prednisolone	NR vs. 30.1	0.79	0.66–0.95	0.015	Elevated liver transaminases, cardiac disorders
	IMPACT [40]	Sipuleucel-T	Placebo	OS improved by 4.1 months	0.78	0.61–0.98	0.03	
	ALSYMPCA [25]	Radium-223 and BSC	BSC	16.1 vs. 11.5	0.69	0.52–0.92	0.01	

BSC: best supportive care; NR: not reached; OS: overall survival.